

Angina-Like Chest Pain as a Symptom of Digestive Tract Disorders

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1. Introduction

Chest pain is a common problem in health care, especially due to its prevalence, the utilization of resources according to the cost of medical procedures, and diagnostic process difficulties. Precordial discomfort occurs in 13-30% of the adult population per year (Cayley, 2005; Dickman & Fass, 2006; Eslick & Talley, 2004; Eslick et al., 2005; Eslick, 2008; Fass, 2008; Fass & Navarro-Rodriguez, 2008; Laird et al., 2004; Ruigómez et al., 2006, 2009), and in 20-40% population during their lifetime (Ruigómez et al., 2006, 2009). About 1.5-5% of the general population seeks a primary care doctor consultation because of chest pain episodes (Cayley, 2005; Erhardt et al., 2002; Eslick, 2008; Fox, 2005; Sheps et al., 2004). Moreover, it is the cause of 634,000 per year cardiologist consultations in the US (Mant et al., 2004), 5% of visits to emergency departments in the UK, and 40% of non-surgical emergency admissions mainly due to acute coronary syndrome suspicion (Ruigómez et al., 2006). Among these patients, only in 15-40% was ischaemic heart disease (IHD) diagnosed on discharge and features of myocardial infarction presented in only 8-10% (Dickman & Fass, 2006; Liuzzo et al., 2005). The analysis by Hollander et al. (2007) has also shown that among patients admitted due to acute coronary syndrome suspicion, myocardial infarction was confirmed in only 4%. Moreover, it has been known for a number of years that about 10-36% of all patients who qualify for coronarography have a normal coronary angiogram (Dickman & Fass, 2006; Dobrzycki et al., 2005; Eslick et al., 2005; Eslick, 2008]. These data corroborate the most recent study by Patel et al. (2010), who conclude that the diagnostic yield of elective coronary angiography (about 20% of all procedures) amounted only to 38% (60% did not influence patients' treatment), in spite of almost 70% of the patients undergoing elective coronary angiography having had positive findings on non-invasive examination (resting electrocardiography, echocardiography, computed tomography, or stress testing). They were also consistent with my recent work, which, among other things, has shown that exercise-provoked chest pain was accompanied by significant ST interval depression in about 60% of subjects with normal coronary angiogram, and 40% of subjects with significant coronary artery narrowing did not present ischaemic-like ECG changes (Budzyński, 2010c).

The above-mentioned data can be summarized as follows:

- non-invasive diagnoses of chest pain and qualification for coronary angiography and percutaneous procedures are still not perfect;
- the most frequent causes of this symptom do not originate in the cardiovascular system; and
- symptom sources other than cardiac should be taken into account more frequently.

On the other hand, these conclusions should not change the prevailing principle that each chest pain episode must be recognized as a potential alarm symptom; the exclusion of life-threatening conditions, including ischaemic heart disease, should remain the basis of chest pain diagnostic procedures. For this reason, it seems a better solution even to overuse coronary angiograms or coronary artery calcification scores (CAC) using multi-slice computer tomography, than miss the detection of severely ill patients. However, it should also always be taken into consideration that invasive cardiological diagnostic procedures give the most benefits to patients with acute chest pain episodes, and in patients with recurrent symptoms, extracardiac sources ought to be more frequently considered (Patel et al., 2010).

It is possible that changes in diagnostic algorithms of chest pain diagnosis and therapy not only decrease the prevalence of this symptom, but might also decrease the costs of health care. Such reductions would be considerable, as the medical procedures connected with chest pain symptoms utilize a noticeable part of health care resources. The annual cost of the medical care of patients with recurrent chest pain in the US ranges from \$350 million to \$1.8 billion (Leise et al., 2010), and has even reached \$3-8 billion (Eslick & Talley, 2004; Eslick et al., 2005; Eslick, 2008; Liuzzo et al., 2005; Mant et al., 2004). In the UK, it consumes approximately 1% of the health care budget (Fox, 2005). However, the real costs of recurrent chest pain are greater because of the social expenditure connected with this symptom (Eslick & Talley, 2004; Eslick et al., 2005; Eslick, 2008; Katerndahl, 2004). Within the one to five-year follow-up period, about 40% of patients with recurrent chest pain are hospitalized at least once due to chest pain, 30% receive a subsequent coronary angiogram (Bugiardini et al., 2005), nearly 30% of patients are unemployed and receive a disability pension, and in 60% of individuals recurrent chest pain limits their physical activity, causing displeasure regarding physicians' competence in 66-81% (Dickman & Fass, 2006).

There may be a number of reasons for unsatisfactory data concerning the prevalence and treatment outcome in patients with recurrent chest pain. To counter this, the many well-known causes of chest pain episodes ought to be analysed, as they have various degrees of clinical importance and may originate from cardiovascular system dysfunction (due to myocardial ischaemia or non-ischaemic reasons), the respiratory system, digestive tract, or begin in the skeleton (Cayley, 2005; Eslick & Talley, 2004; Eslick et al., 2005; Eslick, 2008; Laird et al., 2004). Symptoms deriving from each of these sources may be further aggravated by reactions of depression or panic disorders (Dickman & Fass, 2006; Fass, 2008; Fass & Navarro-Rodriguez, 2008). Moreover, the respective causes of chest pain may coexist and overlap (e.g. the cardiovascular with the gastroenterological or musculoskeletal), and disorders of one system may disturb the function of the others, masking the true cause of symptom evoking. These complicated relationships connected with chest pain make it difficult to diagnose and treat the chest pain source, favour symptom recurrence, and increase resource utilization. Precision in the analysis of symptom characteristics remains the pivotal diagnostic method of chest pain origin because of the aforementioned low diagnostic yield of non-invasive cardiovascular examinations and elective coronarography (Patel et al., 2010). In particular, the localization, radiation and character of chest pain

episodes should be evaluated, as well as any aggravating and alleviating factors (Potts & Bass, 1995; Swap & Nagurney, 2005). Angina pectoris is a particular type of chest pain. It is defined as precordial discomfort, sometimes radiating to the jaw or arm, which is provoked by effort, emotional stress, cold or wind, and withdraws after rest or nitroglycerine use. However, too many times it is forgotten that these criteria are applicable to chest pain episodes originating not only from the cardiovascular system, but also from the digestive tract, especially from the oesophagus, stomach and gall bladder. Moreover, angina pectoris may be caused by myocardial ischaemia, resulting not only from coronary artery narrowing, but also from extracardiac disorders, which leads to an imbalance between myocardial oxygen supply and requirement (e.g. anaemia, thyrotoxicosis). Anaemia is frequently secondary to many digestive tract diseases, such as acute and/or chronic bleeding from the alimentary tract (erosions, ulcers, neoplasm), malabsorption, maldigestion, blood sequestration or autoimmunological reactions. In this way, disorders of the digestive tract can also favour angina pectoris exacerbation. Therefore, although certain elements of the chest pain history are associated with increased (radiating to shoulder(s), or arms, or precipitation by exertion) or decreased (pain like stabbing, pleuritic, positional, or reproducible by palpation) likelihoods of a diagnosis of angina pectoris, none of them alone or in combination identify a group of patients, who do not need a further diagnostic testing (Swap & Nagurney, 2005).

To summarize, angina pectoris is an important, prevalent symptom, utilizing enormous quantities of resources, which is considered all too frequently as a typical symptom of coronary artery disease (CAD), but rarely as a symptom of at least two types of digestive tract disease. The first group concerns diseases which evoke angina-like chest pain from the oesophagus, stomach and gall bladder by the stimulation of their chemo-, mechano-, and/or thermoreceptors; the second group manifests clinically as anaemia, which leads to insufficient oxygen supply to the heart. It is important to realize that both these kinds of digestive tract diseases may overlap with CAD, aggravating precordial symptoms or mimicking atherosclerosis progression. These gastroenterological aspects of angina pectoris will be analysed in this chapter in detail.

2. Epidemiology

Coronary artery disease (CAD) is the most frequent cause of morbidity and mortality in developed countries. As a result of such epidemiological data, almost each chest pain episode is considered as originating from the heart. However, recurrent, angina-like chest pain originating from e.g. the oesophagus is also a frequent problem in everyday practice, mainly due to the high prevalence of alimentary tract diseases in the general population. Recurrent chest pain which is non-cardiac in origin is defined as substernal chest pain in the absence of significant epicardial coronary artery stenoses (Eslick & Talley, 2004; Eslick et al., 2005; Eslick, 2008; Dickman & Fass, 2006; Fass, 2008; Hebbard, 2010; Leise et al., 2010). It is reported every year by about 13-30% of adults, without sex preference. It is experienced during a typical lifespan by approximately 20-40% of the population, with a decrease in prevalence with increasing age (Eslick & Talley, 2004; Eslick et al., 2005; Eslick, 2008; Dickman & Fass, 2006; Fass, 2008; Ruigómez et al., 2006, 2009). The majority of patients with recurrent chest pain which is non-cardiac in origin continue to report episodes of long-term symptoms. In the study by Potts and Bass (1995), 75% of the surviving patients with recurrent chest pain and lack of obstructive coronary artery lesions continued to report the

occurrence of precordial discomfort 11 years later, and 34% reported weekly chest pain symptoms.

The most prevalent cause of non-cardiac chest pain (NCCP) is gastro-oesophageal reflux disease (GERD), which accounts for up to 60% of cases (Leise et al., 2010). The occurrence of its main symptom, heartburn, at least once per month is reported by about 36-44% of the adult population, 14% once per week, and 7% every day (Lemire, 1997). On the other hand, a chest pain sensation is experienced by about 37% of patients with heartburn occurring once per week, 30% of individuals with more seldom symptom occurrence, and about 8% without the feeling of pyrosis (Fass and Navarro-Rodriguez, 2008).

It is generally estimated that gastroenterological abnormalities have a similar prevalence in patients both with and without significant coronary artery narrowing, which shows a possibility to overlap e.g. GERD and CAD symptoms (Budzyński et al., 2008; Budzyński 2010a, 2010c; Cooke et al., 1998; Dobrzycki et al., 2005; Mehta et al., 1996; Ruigómez et al., 2006, 2009; Schofield et al., 1987, 1989). Only a few authors have suggested a lower coexistence of oesophageal disorders in subjects with CAD (Adamek et al., 1999; Battaglia et al., 2005). On the other hand, the probability of diagnosing the respective functional oesophageal disorders (GERD, motility disorders, visceral hypersensitivity) as a cause of non-cardiac chest pain (NCCP) depends on the location of the patient's consultation. They were the cause of non-cardiac chest pain (NCCP) in 0.6-25% of patients of general practitioners, in 46% of patients admitted to Cardiological Intensive Care Units because of acute chest pain, in 60-70% of patients with angina-like chest pain and a normal coronary angiogram, and in 30-80% of patients with obstructive coronary lesions and chronic precordial discomfort non-responsive to optimal anti-angina therapy (Budzyński et al., 2008; Dobrzycki et al., 2005; Rosztóczy et al., 2007; Świątkowski et al., 2004). Therefore, NCCP caused by gastrointestinal, mainly oesophageal, disorders may coexist with CAD in as many as 30-80% of patients. This is very high but clinically very important, as disease overlapping, which causes a great deal of confusion and clinical doubt, is related to at least three factors: the epidemiological, the pharmacological, and the pathophysiological (Budzyński et al., 2008).

Epidemiological causes of the frequent coexistence of digestive and cardiovascular disorders result from a high prevalence of diseases sourced from both systems and have similar risk factors. Both gastroenterological and cardiovascular diseases are found more frequently in older and obese patients, those suffering from hypertension, diabetes, and obstructive sleep apnoea, as well as in smokers, alcohol drinkers and caffeine over-users (Budzyński et al., 2008; Fass & Dickman, 2006;). The frequent coexistence of gastroenterological and cardiovascular diseases also depends on pharmacological causes due to the adverse effects of drugs recommended in the therapy for both system disorders. It is generally known that calcium channel antagonists (e.g. amlodipine, verapamil and diltiazem), nitrates, blockers of alpha-1 adrenergic receptors, and betamimetics may decrease with lower oesophageal sphincter (LOS) pressure and favour gastro-oesophageal reflux, the most frequent cause of NCCP. It should also be taken into consideration that aspirin-induced gastropathy is a potential cause of NCCP (Hsiao et al., 2009). Its symptoms frequently disappear after empirical therapy with proton pump inhibitors (PPIs), but this has not been confirmed by all authors. Moreover, some medicines used in the treatment of gastroenterological disorders may show pharmacological or pharmacodynamic interactions with drugs recommended for cardiovascular diseases, e.g. omeprazole decreases the bioavailability of digoxin, warfarin and clopidogrel. The last interaction in particular caught the investigator's attention following publication by Juurlink et al. (2009), who reported a greater prevalence of acute

coronary syndromes and myocardial infarction in patients taking omeprazole, rabeprazole or lansoprazole for the purpose of preventing gastrointestinal bleeding during dual anti-platelet therapy. Although recent publications have not confirmed the clinical importance of this interaction, their authors and panels of experts have recommended caution in co-prescribing PPIs with clopidogrel (American College of Cardiology Foundation [ACCF], 2010; American Society for Gastrointestinal Endoscopy [ASGE], 2009; Bhatt et al., 2008; de Aquino Lima & Brophy, 2010; Laine & Hennekens, 2010). There is also divergent information concerning the interaction between PPIs and acetylsalicylic acid, showing no effect (Adamopoulos et al., 2009), an increase (Kasprzak et al., 2009), and a decrease (Würtz et al., 2010) in anti-platelet aspirin activity.

Finally, the high prevalence of the coexistence of cardiovascular and gastroenterological chest pain causes may also result from pathophysiological factors, mainly the inflammatory and neural pathways for linked angina (Chauhan et al., 1996; Hoff et al., 2010; Makk et al., 2000; Rosztóczy et al., 2007). They are connected in the mechanism of a vicious circle, in which gastro-oesophageal reflux induces myocardial ischaemia, and products of the anaerobic myocardial metabolism due to ischaemia in turn provoke gastro-oesophageal reflux, dysphagia, or hiccups (Hoff et al., 2010; Krysiak et al., 2008; Stec et al., 2010). These problems are explained in detail in a separate subsection (4b).

3. Prognosis

Patients with recurrent chest pain and normal coronary angiogram (i.e. NCCP) have a relatively good life expectancy prognosis. The 30-day mortality connected with this symptom is estimated at 0.3-1.1% (Eslick & Talley, 2004; Eslick et al., 2005; Eslick, 2008), the risk of major cardiovascular event (death, myocardial infarction) with an odds ratio (OR) amounting to 2.3 (95% CI, 1.3-4.1) (Ruigómez et al., 2006, 2009), and the need for emergency coronary intervention amounting to approximately 4% (Hollander et al., 2007). However, in the recent study by Leise et al. (2010), patients with NCCP which is gastrointestinal in origin displayed less overall survival at all time points compared with their counterparts with NCCP of unknown origin, specifically 70.1% at 10 years and 51.8% at 20 years. This was mainly explained by the overlapping of cardiovascular risk factors in patients with GERD. Whereas, in the paper by Munk et al. (2008), the 10-year relative risk of hospitalization for ischaemic heart disease (a discharge diagnosis of myocardial infarction, angina and/or heart failure) following a normal upper endoscopy among 386 Danish patients with unexplained chest/epigastric pain was 1.6 (95% CI, 1.1-2.2), compared with 3,973 population controls. The adjusted mortality rate ratio was the greatest within the first year after an upper endoscopy and amounted to 2.4 (95% CI, 1.3-4.5). The difference faded with time, and the 10-year adjusted mortality rate ratio amounted to 1.1 (95% CI, 0.9-1.5). The increased mortality among these patients stemmed from alcohol dependence, pneumonia (not as a complication of the endoscopy), and lung cancer, but not IHD.

On the other hand, patients with recurrent chest pain have a poor prognosis in relation to symptoms receding. They also present a high annual rate (50-81%) of chest pain recurrence (Ruigómez et al., 2006, 2009). Unemployment connected with this symptom occurrence concerns 41-50% of patients (Eslick & Talley, 2004; Eslick et al., 2005; Eslick, 2008; Fass, 2008; Fass & Dickman, 2006; Fass & Navarro-Rodriguez, 2008).

The aforementioned data justify undertaking the effort to establish the most precise diagnosis of the source of recurrent chest pain. Such a procedure makes it possible to calm

the patient by explaining some of the non-dangerous reasons for chest pain occurrence. Moreover, the diagnosis of the real source of distressing complaints makes possible a specific treatment recommendation. It is effective in different degrees in about 80% of patients, decreasing NCCP episode recurrence and hospitalization necessity, improving patients' health-related quality of life, and reducing the health care costs (Cheung et al., 2009; Dickman & Fass, 2006; Fass, 2008; Fass & Dickman, 2006; Fass & Navarro-Rodriguez, 2008; Laheij et al., 2003; Sheps et al., 2004). The diagnosis of GERD as a source of NCCP and the recommendation of the prolonged use of PPIs has decreased the risk of chest pain recurrence by 46% and the number of patients needing to be treated (NNT) has amounted to 3 (95%CI, 2-4) (Cremonini et al., 2005). Whereas, undiagnosed chest pain has been shown to increase the risk of hospitalization due to CAD and all-cause mortality during 10 years of follow-up (Munk et al., 2008).

4. Pathophysiology

As has been mentioned, angina-like chest pain presents typical features of visceral pain which may be symptomatic of both ischaemic heart diseases and digestive tract disorders. To the first group of diseases belong both patients with coronary artery narrowing, known as patients with CAD, and subjects with a normal or almost normal coronary artery angiogram ("non-visible", "non-obstructive atherosclerotic coronary disease" (Bataglia et al., 2005). Chest pain occurring in patients with a normal coronary angiogram is frequently called NCCP. It may be caused by extracardiac diseases, mainly digestive tract disorders (Labenz, 2010). However, it should also be taken into account that it may also be sourced by missed coronary angiogram lesions, microvascular coronary dysfunction (cardiac syndrome X), coronary spasm, or secondary angina (e.g. aortic valve dysfunction, tachycardia, thyrotoxicosis, anaemia) (Bugiardini et al., 2005).

The relationships between the digestive tract and cardiovascular system are complicated and stem from epidemiological, pharmacological (described above) and pathophysiological factors. Each of them concerns both patients with a normal coronary angiogram and with CAD, and may lead to symptom mimicry and overlapping. There are at least three pathomechanisms evoking angina-like chest pain in the course of digestive tract diseases:

- a. chest pain is evoked by stimulation of digestive tract pain receptors and mimics angina;
- b. digestive tract diseases via neural and inflammatory pathways disturb myocardial perfusion and evoke chest pain which is cardiac in origin due to myocardial ischaemia, although the true cause of the symptoms is located e.g. in the oesophagus;
- c. chest pain, cardiac in origin, is secondary to an imbalance between oxygen supply and myocardial demand due to anaemia, which is frequently secondary to various diseases of the alimentary tract.

4.1 Angina-like chest pain which is digestive tract in origin

The most common example of the first pathophysiological group of chest pain is GERD, responsible for 50-60% of the causes of NCCP (Dickman & Fass, 2006; Eslick & Talley, 2004; Eslick et al., 2005; Eslick, 2008; Fass & Dickman, 2006; Fass & Navarro-Rodriguez, 2008; Hebbard, 2010; Tipnis et al., 2007; Tougas et al., 2001). The main symptoms of GERD are heartburn (pyrosis), regurgitation, or the "reflux chest pain syndrome" distinguished by the

definition and classification of GERD developed by the Montreal Consensus Group in 2006 (Vakil et al., 2006). The other diseases which may mimic angina pectoris, frequently known as non-GERD-related NCCP, are as follows: oesophagitis caused by non-reflux-related factors (such as infections or being drug induced); oesophageal motility disorders; hiatal hernia; gastric and duodenal ulcer disease; drug- (aspirin, non-steroidal anti-inflammatory drugs) induced gastropathy; acquired hepato-diaphragmatic migration of the hepatic flexure of the colon (Chilaiditi's syndrome); cholecystitis; and acute pancreatitis (Dickman & Fass, 2006; Drewes et al., 2006; Eslick & Talley, 2004; Eslick et al., 2005; Eslick, 2008; Fass & Dickman, 2006; Fass & Navarro-Rodriguez, 2008; Ruigómez et al., 2006, 2009, Sorrentino et al., 2005). The Rome Criteria III also distinguish a particular kind of non-cardiac chest pain, called "functional chest pain of presumed oesophageal origin", which is defined as midline discomfort which is not of burning quality, lasting at least three months, with an onset at least six months prior to diagnosis, and an absence of GERD and histopathology-based oesophageal motility disorders (Drossman, 2006). My own observations have also shown that exercise-induced oesophageal motility disorders, such as exercise-provoked oesophageal spasm (EPOS) or exercise-provoked gastro-oesophageal acid reflux, may play some role in the pathogenesis of angina-like chest pain in at least 22% of patients with recurrent symptoms (Budzyński, 2010a, 2010b). It is worth underlining that nearly 80% of the patients with functional chest pain simultaneously present symptoms of other functional disorders, primarily irritable bowel syndrome (27%) and abdominal bloating (22%) (Dickman & Fass, 2006; Fass & Navarro-Rodriguez, 2008). Their coexistence with chest pain may help in appropriate diagnoses. The aforementioned mainly oesophageal and gastric abnormalities may be accompanied by endoscopically visible morphological changes in mucosa or not. Some of these differences in the clinical course of GERD have been classified by the Global Consensus Group in Montreal, which, among oesophageal syndromes, enumerates: (a) symptomatic syndromes (without oesophageal erosions) concerning approximately 60% of patients, and (b) syndromes with oesophageal injury (erosive oesophagitis, oesophageal strictures, Barrett's oesophagus, oesophageal adenocarcinoma) (Sarkar et al., 2004; Vakil et al., 2006). In this way, oesophageal erosions are present in 10-70% of patients with NCCP (Fass and Navarro-Rodriguez, 2008); therefore, a lack of endoscopic abnormalities does not exclude both a GERD and an oesophageal origin of NCCP.

The above-mentioned diseases of the oesophagus, stomach, colon, pancreas or gall bladder evoke angina-like chest pain by the activation of local pain receptors, both chemical and mechanical (e.g. ASIC, TRPV, P2X and TREK), by inflammatory mediators, kinins, pepsin, bile acids, changes in oesophageal pH, pressure (oesophageal distension, volume, shear stress), or temperature, and by the induction of a secondary local motility response, expressed by hypermotility, oesophageal long muscle shortening, high amplitude oesophageal peristalsis, oesophageal distension or prolonged oesophageal contractions (Drewes et al., 2006; Sifrim et al., 2007; Tipnis et al., 2007). However, the intensity of the clinical manifestation of these disorders is related to the threshold of receptor stimulation. Its decrease is frequently known as visceral hypersensitivity (Dickman & Fass, 2006; Drewes et al., 2006; Eslick & Talley, 2004; Eslick et al., 2005; Eslick, 2008; Fass & Dickman, 2006; Fass & Navarro-Rodriguez, 2008). It is enumerated as one of the main pathomechanisms of symptoms in the course of cardiac syndrome X, mitral prolapse syndrome, irritable oesophagus, functional dyspepsia, irritable bowel syndrome (IBS), and fibromyalgia (Katerndahl, 2004; Hammet et al., 2003; North et al., 2007). The recently published investigation by Nasr et al. (2010) using a balloon distension test has shown that

oesophageal hypersensitivity plays an important role in 75% of patients with functional (non-cardiac and non-reflux) chest pain. The basis of this disorder is a decrease in the pain threshold, both at the central and peripheral perception levels (Dickman & Fass, 2006; Fass & Dickman, 2006; Sheps et al., 2004; Sifrim et al., 2007). The range of the change in this threshold may be modulated by a number of factors influencing the function of the brain-gut axis (Mayer & Tillisch, 2011; Sheps et al., 2004). These factors are as follows:

- personal (female gender, age between 15-34, incorrect response of the autonomic nervous system, psychiatric disorders, stress, sleep disturbances, oesophagitis or gastritis, mucosal mastocyte infiltration, allodynia);
- environmental (stress, *Helicobacter pylori* (Hp) infection, dietary factors, especially a fatty diet) (Remes-Troche, 2010; Sheps et al., 2004; Sifrim et al., 2007; Tougas et al., 2001).

The modulation of the central pain threshold in patients with unexplained chest pain, CAD and occult GERD may also be related to chronic receptor stimulation and/or the coexistence of psychiatric disorder (Drewes et al., 2006; Lenfant, 2010; Remes-Troche, 2010). Sarkar et al. (2004) have reported a decrease in allodynia after therapy with PPIs. Whereas, Makk et al. (2000) have shown a greater oesophageal acid sensitivity (a lower pain threshold) in individuals with a normal coronary angiogram and patients undergoing coronary angioplasty than in those with coronary artery narrowing and undergoing coronary angiography alone. Moreover, in approximately 70% of patients with NCCP, anxiety, depression or somatization have been observed (Dickman & Fass, 2006; Eslick & Talley, 2004; Eslick et al., 2005; Eslick, 2008; Fass & Dickman, 2006; Fass & Navarro-Rodriguez, 2008; Katerndahl, 2004). In these subjects, NCCP amelioration and a decrease in pain hypersensitivity were found after therapy with antidepressants such as imipramine, sertraline or trazodone in controlled and uncontrolled investigations (Dickman & Fass, 2006; Eslick & Talley, 2004; Eslick et al., 2005; Eslick, 2008; Fass & Dickman, 2006; Fass & Navarro-Rodriguez, 2008). Psychiatric disorders, besides decreasing the pain threshold, may also evoke chest pain by hyperventilation and secondary coronary arteries and/or oesophageal spasm (Chauhan et al., 1996). As a result, the following markers of a psychiatric basis for recurrent chest pain were proposed: atypical character of symptoms, female gender, younger age, a high level of anxiety, and a neurotic personality (Ringstrom and Freedman, 2006).

The character of the pain occurring in the course of digestive tract diseases may be similar to that of acute coronary syndrome or recurrent stable angina pectoris. The simple explanation of this fact involves the visceral features of the pain and the anatomical localization of the heart and oesophagus in the chest. The latter factor causes the overlap of the head areas in brain sensory representations of the oesophagus and heart. However, the anatomical relationships between the oesophagus and the heart may produce symptoms in some more immediate way. Namely, the extended left atrium, due to e.g. mitral valve disease or left ventricle cardiac failure, may press the oesophagus, evoking changes in intra-oesophageal pressure, mechanical receptor stimulation or disturbance in the oesophageal passage, known as cardiac dysphagia or odynophagia (angina-like chest pain which is oesophageal in origin). These disorders may also, through pressure receptor stimulation, activate vagal neural reflexes leading to a decrease in myocardial perfusion (angina-like chest pain which is cardiac in origin), described in detail in part b of this section. On the other hand, an enlarged oesophagus, due to e.g. achalasia or oesophageal carcinoma, producing left atrium compression, may also evoke local ischaemia of the atrial muscle and/or activation of mechano-electrical coupling, raising the local dispersion in the functional potential of atrial

muscle cells and producing re-entry loops. These disorders may manifest clinically as chest pain or arrhythmia (Budzyński & Pulkowski, 2009; Duygu et al., 2008; Upile et al., 2006).

To summarize, chest pain originating from the oesophagus may be similar to cardiac-derived angina pectoris. It may be caused by activation receptors in the digestive tract and motor dysfunction of the oesophageal wall. The intensity of the clinical manifestation of these disturbances is modulated by the frequent presence of visceral hypersensitivity. These complicated relationships have explained the confusion and misdiagnosis often accompanying chest pain diagnosis.

4.2 Angina-like chest pain which is cardiac in origin but induced by digestive tract disorders

Apart from the above-mentioned resemblance of chest pain originating from the heart and the oesophagus, as well as the overlapping of symptoms evoked both by cardiovascular and alimentary tract diseases, the clinical doubts concerning the true source of chest pain, whether cardiac or oesophageal, are augmented by the second of the distinguishing pathomechanisms of chest pain caused by diseases of the digestive tract: the activation of neural and inflammatory pathways which in turn may decrease myocardial perfusion.

Neural reflex loops between the heart and oesophagus have been found both in human and animals. Stimulation of oesophageal chemo-, mechano- and thermoreceptors, apart from provoking chest pain of oesophageal origin in about half (49-56%) of patients with a normal coronary angiogram (cardiac syndrome X), coronary artery spasm or obturative lesions in coronarography (patients with CAD), may also activate vagally-mediated, viscerovisceral neural reflexes (e.g. cardio-oesophageal reflex) (Budzyński et al., 2008; Budzyński, 2010c; Charng et al., 1988; Chauhan et al., 1996; Dobrzycki et al., 2005; Drewes et al., 2006; Fass & Dickman, 2006; Makk et al., 2000; Manfrini et al., 2006; Rasmussen et al., 1986; Rosztóczy et al., 2007) or a viscerosomatic neural reflex (Drewes et al., 2006; Jou et al., 2002). The first reflex may evoke ischaemic chest pain, cardiac in origin, resulting from diminished myocardial perfusion and secondary to pre-arteriole contraction (Chauhan et al., 1996; Makk et al., 2000; Rosztóczy et al., 2007); the second, viscerosomatic reflex, causes an increase in the spinotrapezius muscle contractions both after cardiac and oesophageal receptor stimulation via convergent pathways in the sympathetic nerves (Jou et al., 2002). The last reflex is responsible for the somatic component of pain evoked by the stimulation of visceral, cardiac or oesophageal receptors. Moreover, afferent stimulus originating from the oesophagus, stomach or gall bladder may also interfere with stimulus derived from the heart in the spinal cord, which is a further cause of the resemblance of symptoms deriving both from the digestive tract and the cardiovascular system (Sheps et al., 2004).

However, the aforementioned reflexes (neural loops) do not function in all subjects but only in about half (Chauhan et al., 1996; Makk et al., 2000; Mehta et al., 1996; Rosztóczy et al., 2007); this results from the modulation of the impulse transmission along nervous pathways by coexistent mental or psychiatric disorders, the balance between the sympathetic and parasympathetic parts of the autonomic nervous system and the threshold of receptor stimulation, which is decreased in patients with visceral hypersensitivity. These suggestions are supported by papers showing a relatively high prevalence of panic or depressive disorders in approximately half of patients, with both cardiovascular and digestive tract diseases (Lenfant, 2010). Autonomic nervous system imbalance has also been found in up to half of patients with functional chest pain (Nasr et al., 2010; Tougas et al., 2001), *Helicobacter*

pylori infection (Budzyński et al., 2004), functional dyspepsia, irritable bowel syndrome (Mayer & Tillisch, 2011), or chronic heart failure. Modulation of visceral reflex activity by these cofactors may cause the activity of cardio-oesophageal reflexes not to manifest clinically in all subjects. Dobrzycki et al. (2005) have suggested that those most susceptible to the clinically important effect of cardio-oesophageal reflex activity seem to be patients with CAD, because in this patient group even slight coronary reserve impairment may be clinically important. On the other hand, Rosztóczy et al. (2007), using a combination of an oesophageal acid perfusion test and transoesophageal Doppler echocardiographic coronary flow measurement, have shown that 49% of subjects presented coronary spasm in response to oesophageal acidification more frequently than either epicardial coronary artery disease or microvascular coronary disease, probably due to signs of cardio-oesophageal reflex activation. In the gastroenterological work-up, they had higher DeMeester scores, an increased number of reflux episodes, a fraction time below pH 4, and prolonged acid reflux episodes. These data corroborate the paper by Sarkar et al. (2004), who observed the reversible influence of chronic oesophageal mucosa exposure to acid on the visceral pain threshold, one of the mechanisms modulating visceral, vagally-mediated reflex activity. The importance of the role of the parasympathetic nervous system for subjects with NCCP has also been shown by Tougas et al. (2001). In their study, 67% of patients with a normal coronary angiogram presented angina-like chest pain after oesophageal acid infusion. Chest pain in "acid-sensitive patients" was accompanied by a higher baseline heart rate and lower baseline vagal activity (estimated using heart rate variability [HRV] analysis) than "acid-insensitive patients". During acid infusion, vagal cardiac outflow (expressed as a high frequency component of HRV) increased in "acid-sensitive" but not in "acid-insensitive" patients (Tougas et al., 2001).

The endpoint of the aforementioned complicated influence of the nervous system on the interrelationships between the cardiovascular and alimentary systems is myocardial ischaemia, which may manifest clinically in 49-56% of patients as angina pectoris, arrhythmia and syncope (Chauhan et al., 1996; Cubattoli et al., 2009; Cuomo et al., 2006; Makk et al., 2000; Mehta et al., 1996; Rosztóczy et al., 2007). This symptomatic decrease in myocardial perfusion after oesophageal stimulation by acid was produced by epicardial coronary artery spasm (Rosztóczy et al., 2007) or by contraction of the prearterioles (Chauhan et al., 1996). The neural pathway for these effects (so-called linked angina) was proven by the lack of similar perfusion changes in heart transplant recipients (Chauhan et al., 1996). However, the aforementioned reflexive decrease in myocardial perfusion was accompanied by ischaemic electrocardiographic (ECG) changes in only a few works (Budzyński et al., 2008; Dobrzycki et al., 2005; Rosztóczy et al., 2007; Singh et al., 1992; Świątkowski et al., 2004).

However, the above-described mechanism is only the first on the arc of the cardio-oesophageal loop of feedback. The second, opposite arm of this loop may be stimulated by the products of anaerobic myocardial metabolism, mainly bradykinin (Caldwell et al., 1994; Krysiak et al., 2008), invasive cardiac manoeuvres, manipulation, coronary angioplasty (Makk et al., 2000) or cardiac arrhythmia (Stec et al., 2010). Such activation may lead to reflexive oesophageal motility disorders or a decrease in lower oesophageal sphincter (LOS) pressure, which facilitates gastro-oesophageal reflux occurrence, changes in oesophageal pH, potential reflexive activation of a cardio-oesophageal reflex and a reduction in myocardial perfusion (Caldwell et al., 1994). Described as reflexive, bidirectional, neuro-hormonal mechanisms connect the pathogenesis of the digestive tract and cardiovascular

diseases in a vicious circle. Moreover, some studies have shown that the described associations between oesophageal and vascular spasm may also result from myogenic mechanisms and may be an overall effect of smooth muscle hypercontractility, depending on the individual concerned (Adamek et al., 1998a, 1998b, 1999; Makk et al., 2000; Manfrini et al., 2006; Rasmussen et al., 1986). The myogenic component of coronary-oesophageal interrelationships has been suggested by the coexistence of oesophageal spasm alongside coronary artery spasm, hypertension, migraine and Raynaud's symptoms.

The occurrence of angina-like chest pain, as well as other cardiac symptoms such as arrhythmia, or syncope may also be secondary to inflammatory factors often deriving from the digestive tract. The role of inflammatory processes in cardiovascular disease pathogenesis has been investigated for many years. At least two mechanisms have been distinguished for the influence of inflammation on cardiac function: local and systemic. The first has been mentioned by Weigl et al. (2003), who have suggested the possibility of local inflammatory process propagation through the oesophageal wall producing local pericarditis or atrial myocarditis. These histological abnormalities can be a substrate of chest pain or arrhythmia (Navarese et al., 2010; Stölberger & Finsterer, 2003). However, there is more to be said for the role of a systemic inflammatory response in the pathogenesis of chest pain which is cardiac in origin but evoked or intensified by digestive tract diseases. Systemic inflammatory factors known as cytokines (e.g. TNF-alpha, IL-1, IL-6) or adhesion molecules (e.g. VCAM-1, ICAM-1) are involved in the pathogenesis of atherosclerosis, endothelial dysfunction, and cardiac arrhythmia, mainly atrial fibrillation. Their synthesis may be stimulated in the course of many of the diseases of the alimentary tract, such as periodontal diseases, oesophagitis, gastritis, ileitis, inflammatory bowel diseases, liver cirrhosis, pancreatitis, and neoplasm (Shanker & Kakkar, 2009; Stölberger & Finsterer, 2003). Some reports, including my own data, have also shown the unfavourable effect of *Helicobacter pylori* infection, not only on the course of digestive tract diseases, but also on the course of recurrent angina-like chest pain (Budzyński, 2011), changes in autonomic nervous system balance (Budzyński et al., 2004) and atherosclerosis progression (Franceschi et al., 2009). CagA seropositivity has been significantly and positively associated with the occurrence of acute coronary events, atherosclerosis progression and arrhythmia prevalence (Bunch et al., 2008a, 2008b; Franceschi et al., 2009; Miyazaki et al., 2006). The positive relationship between Hp infection and cardiac syndrome X (Celik et al., 2010; Eskandarian et al., 2006; Rasmi & Raeisi, 2009) has also been reported but not confirmed by others (Saleh et al., 2005). Whereas, Sandifer et al. (1996), based on the results of the EUROGAST Study Group, had shown a negative association between the seroprevalence of antibodies to Hp and the death rate from ischaemic heart disease.

Numerous mechanisms for the influence of Hp on atherosclerosis complications have been suggested. They may act directly on atherosclerotic plaques, as suggested by the results of Kowalski et al. (2001), who revealed the presence of Hp DNA in atherosclerotic lesions and an increase in coronary artery diameter after microorganism eradication. It has also been implied that mimicry occurs between the cytotoxin-associated gene-A (CagA) antigen expressed by some Hp strains and the protein presented in atherosclerotic plaques (Franceschi et al., 2009). Hp infection, similarly to periodontal infection (Shanker & Kakkar, 2009) or the hepatitis C virus (Ramdeen et al., 2008), may also act as one amongst a number of factors taking part in the mechanisms of pathogen burden through the following: non-specific inflammatory pathway stimulation (e.g. hs-CRP increase); the induction of endothelial and microvascular dysfunction; an increase in adhesion molecule expression

(e.g. VCAM-1, ICAM-1); the over-synthesis of pro-atherogenic cytokines (e.g. IL-1 beta, IL-6, TNF-alpha); changes in autonomic nervous system balance (Budzyński et al., 2004; Budzyński, 2011; Celik et al., 2010; Rasmi & Raeisi, 2009); and the production of metabolic abnormalities, such as hypertriglyceridaemia, increased LDL cholesterol levels, plasma lipid oxidation, hyperfibrinogenaemia, altered blood coagulation and leukocytosis. The role of Hp infection as a cause of myocarditis and ECG changes in patients with persistent chest pain has also been reported (Navarese et al., 2010). Apart from the aforementioned mechanisms, Hp infection may also affect the occurrence of angina-like chest pain which is gastroenterological in origin, being one of the pathogenic factors of gastritis, gastric and duodenal ulcer disease. Hp infection may also play a role in GERD pathogenesis via impaired vagal control of LOS pressure and a decrease in the release of ghrelin, a prokinetic hormone (Thor & Blaut, 2006).

The described systemic inflammatory process mediators, e.g. deriving from the digestive tract, could influence cardiac symptom occurrence, not only by direct action on the vascular wall, but also via neuroimmune- endocrine crosstalk (Collins et al., 2009; Grundy et al., 2006; Marques et al., 2010; Wood, 2007). Inflammation mediators, especially cytokines such as TNF-alpha, interleukin-1 and interleukin-6, may stimulate both the hypothalamus and brain stem. The outcome of the first is the activation of the pituitary-suprarenal axis, which leads to increased cortisol and adrenalin secretion, and of the second is sympathetic activation. The consequence of such neuroendocrine stimulation may be chest pain, myocardial infarction, arrhythmia, sudden death or an increase in intestinal permeability due to digestive tract ischaemia. Its effect may in turn be an increase in cytokine secretion and the activation of immunological cells: lymphocytes, monocytes, macrophages and granulocytes possessing surface receptors for a number of neuroendocrine products. These can then stimulate vessel walls, induce endothelial dysfunction, atherosclerotic plaque instability and in turn produce neuroendocrine imbalance (Marques et al., 2010; Saleh et al., 2005). In this way, the aforementioned relationships involve the cardiological and gastroenterological symptoms in the second neuroimmune-endocrine vicious circle mechanism.

In summary, neural loops, inflammatory processes and neuroimmune-endocrine crosstalk activated by digestive tract disorders may be the second group, in addition to digestive tract abnormalities, of important factors evoking chest pain which is cardiac in origin. It may result from myocarditis and/or a progression or reversible reduction in myocardial perfusion. These processes may play a role in patients both with and without significant coronary artery narrowing.

4.3 Angina-like chest pain which is cardiac in origin but secondary to anaemia caused by diseases of the alimentary tract

The main cause of ischaemic heart disease and its typical symptom of angina pectoris is an imbalance between coronary blood supply and myocardial requirement. This shows that besides a decrease in blood delivery to the myocardium, angina-like chest pain may also be evoked or exacerbated by inadequate oxygen supply due to anaemia. Rapidly or slowly progressing anaemia may be a symptom of many digestive tract diseases, both of the upper and lower parts. It may be an effect of bleeding, malabsorption, maldigestion, blood sequestration or autoimmunological reactions (Zhu et al., 2010). For this reason, diagnostic procedures for the digestive tract, including biochemical and serological examinations, ultrasonography, panendoscopy, colonoscopy, and in special cases capsule endoscopy and single or double balloon enteroscopy, should be recommended for each male,

postmenopausal women, and younger females when the quantity of blood loss during menstruation is insufficient to explain the presence of anaemia (Zhu et al., 2010).

However, both cardiologists and gastroenterologists should also take into account that acute bleeding into the digestive tract or slowly progressing iron deficiency anaemia may also be a symptom of the haemorrhagic complications of the anti-thrombotic therapy (e.g. aspirin, clopidogrel, heparin, bivalirudin, etc.) which is fundamental in the treatment of acute coronary syndromes and stable angina pectoris (Dai et al., 2009; Nema et al., 2008). Of these complications, 50% occur in the digestive tract (To et al., 2009). Prior to endoscopic procedures, especially with a high risk of haemorrhagic complications (e.g. polypectomy or mucosal resection), the risk of the discontinuation of dual anti-platelet therapy in particular should be estimated (ASGE, 2009; ACCF, 2010; Bhatt et al., 2008). This is very important, as clopidogrel withdrawal may lead to cardiac stent thrombosis in 15-40% of cases; it is associated with a myocardial infarct rate of 50% and a related death rate of approximately 20% (ASGE, 2009). Therefore, in such clinical situations, consultation between cardiologist and gastroenterologist is needed to avoid patients being treated from a single organ perspective of the relative risks (cardiology vs. gastrointestinal) but with a more global balanced risk assessment instead to optimize patient outcomes.

The above deliberation shows the need for accuracy in evaluating angina pectoris symptom pathomechanisms (primary or secondary) to avoid the iatrogenic, clinically overt or silent haemorrhagic complications of anti-thrombotic drugs. Misdiagnosis or the inadequate taking of a medical history may lead to anaemia occurrence or aggravation, an increase in chest pain severity, unnecessary coronary angiogram performance, or death during haemorrhagic shock. One potential clinical scenario may take the following course: angina pectoris (stable or acute coronary syndrome) + latent digestive tract disease → treatment with aspirin and clopidogrel and/or warfarin or heparin → haemorrhagic complications (clinically overt or silent) → secondary anaemia and/or haemodynamic complications → exacerbation of chest pain severity → coronary angiogram performance, percutaneous coronary intervention and the need for prolonged dual anti-platelet therapy → an increase in the intensity of bleeding from the digestive tract, anaemia aggravation and a further increase in angina pectoris severity. In this way, clinically overt or latent bleeding from the digestive tract and secondary anaemia, besides the aforementioned neural cardio-oesophageal loop and neuroimmune crosstalk, may be the third vicious circle mechanism, in which gastroenterological disorders, exacerbated or complicated by anti-platelet or anti-thrombotic treatment, may increase angina pectoris severity.

5. Diagnosis

According to current opinion, all patients with chest pain should first be evaluated for a cardiac cause of their symptoms (Fass & Dickman, 2006; Potts & Bass, 1995). To make this easier, some authors recommend estimating the probability of cardiac chest pain origin on the basis of tests with nitroglycerine and the number of atherosclerosis risk factors. In spite of some doubts concerning the low specificity of a nitroglycerine test (Fass & Dickman, 2006), chest pain disappearance within five minutes after one dose of 400 mcg of short-acting nitrates, a cardiac or gastroenterological symptom source should be considered, rather than a psychiatric one. Afterwards, if the tests present more than two atherosclerosis risk factors, a cardiological diagnostic pathway should be taken first (an ECG, stress test, stress echocardiography and angiography being the proposed series of steps). However, if

patients have fewer than three risk factors, the following sequence of procedures in the diagnosis of angina-like chest pain presumed to be of oesophageal origin is proposed: complete the Carlsson-Dent questionnaire; empirical therapy with proton pump inhibitors (PPIs), known as the "omeprazole test"; endoscopy; 24-hour ambulatory oesophageal pH-metry; 24-hour multichannel intraluminal oesophageal impedance with pH-metry examination, in particular with an analysis of the symptom index (SI) or symptom association probability (SAP); stationary oesophageal manometry; 24-hour oesophageal manometry with SI or SAP evaluation; brain imaging; as well as psychiatric examination (Dickman & Fass, 2006; Eslick & Talley, 2004; Eslick et al., 2005; Eslick, 2008; Fass & Dickman, 2006; Fass & Navarro-Rodriguez, 2008; Hewson et al., 1990; Oranu and Vaezi, 2010; Sheps et al., 2004). The recently proposed diagnostic methods for NCCP presumed to be of oesophageal origin are as follows: a magnifying endoscopy with high resolution imaging (to show oesophageal mucosa microerosions), prolonged oesophageal pH-metry using the wireless Bravo method, high resolution manometry, high frequency intraoesophageal ultrasonography (HFIUS), impedance planimetry, and multi-slice computer tomography. However, their usefulness in the diagnosis of chest pain requires confirmation (Dickman & Fass, 2006; Fass & Dickman; George & Movahed, 2010; Hebbard, 2010).

The Carlsson-Dent questionnaire (CDQ) is a simple but old diagnostic tool for the detection of GERD, the main cause of NCCP without alarm symptoms or the suspicion of the other possible GERD complications (Numans & de Wit, 2003). It has been validated in European patients. In comparison with oesophageal pH-metry and endoscopy, it is estimated as having good sensitivity (89-94%) and a positive predictive value (55-90%) for the detection of GERD.

Empirical therapy with a triple standard dose of PPI (e.g. 40-0-20 mg of omeprazole) gives valuable information about GERD being the reason of NCCP. It is a simple, available, sensitive and cost-effective tool, but the specificity is insufficient to put this test into practice as the single objective diagnostic criterion, mainly due to risks connected with false undiagnosed CAD. Its sensitivity and specificity in the diagnosis of GER-related chest pain in comparison with oesophageal pH-metry reaches 69-95% and 57-86% respectively (Fass & Dickman, 2006; Dickman et al., 2005; Wang et al., 2005). However, this test may be less valuable for patients in whom symptoms appear less frequently than twice a week (Cremonini et al., 2005). On the other hand, taking this limitation into account, testing with PPIs can be used as a diagnostic (lasting 1-2 weeks) and as a diagnostic-therapeutic test (1-4 months of "therapy as investigation"). Chest pain disappearance after the respective period should be interpreted as confirmation of clinical associations between acid regurgitation and symptom occurrence. The economic aspects of NCCP diagnosis also see much of the use of this test in clinical practice. A one-week test with PPI decreased the overall costs of NCCP diagnosis by \$573-1,338, mainly due to the reduction in the number of panendoscopies performed (by 81%), 24-hour oesophageal pH-metry (by 79%), and remains the functional diagnostic examination for NCCP (Fass & Navarro-Rodriguez, 2008). Unfortunately, this test was not validated in patients with CAD, in whom GERD symptom prevalence and overlapping seems to be clinically important. Of this group, GERD-related chest pain episodes were found in 30-46% of patients (Budzyński et al., 2008; Dobrzycki et al., 2005). These overlapped with chest pain of cardiac origin, being indistinguishable from angina pectoris resulting from myocardial ischaemia and leading to symptom persistence. In the RITA-3 study, 24% of participants still reported angina in the II-IV class according to the CCS classification over one year after percutaneous coronary intervention (Kim et al., 2005;

Poole-Wilson et al., 2006). In light of this, such empirical testing with PPIs seems to be worth recommending for each patient with refractory angina. Unfortunately, the recent recommendation concerning refractory angina by Kones (2010) does not refer to such a possibility. However, due to possible potential dangerous interactions between clopidogrel and PPIs, this test should be avoided in patients on dual anti-platelet therapy (ACCF, 2010; Bhatt et al., 2008). Our own investigations have also shown the necessity for careful interpretation of testing with PPIs due to an increase found in nitric oxide bioavailability after rabeprazole therapy (Kłopocka et al., 2006) and beta-endorphin plasma levels (Budzyński et al., 2010). These substances produced during therapy with PPIs may mask the true chest pain source, including that of cardiac in origin.

Endoscopy is the most recommendable exploratory procedure in patients with GERD symptoms, fundamentally heartburn and regurgitation, especially when alarm symptoms appear. On the other hand, 50-75% of GERD and 10-70% of NCCP patients have a normal endoscopy examination (non-erosive GERD) (Dickman & Fass, 2006; Fass & Dickman, 2006). The recent report by Dickman et al. (2007a), on the basis of the results of upper endoscopy undergone for NCCP and GERD in a group of respectively 3,688 and 32,981 consecutive patients, has shown a normal upper endoscopy in 44.1% of NCCP patients and 38.8% of those with GERD. Of the NCCP group, 28.6% had a hiatal hernia, 19.4% erosive oesophagitis, 4.4% Barrett's oesophagus, and 3.6% stricture/stenosis. Peptic ulcers were found in 2% of the NCCP patients. Thus, endoscopy does not appear to be dispensable in a large group of patients with NCCP. It is likely that the new generation of endoscopy equipment - magnifying endoscopy - would be helpful in the detection of oesophageal mucosa microerosions, but it is unable to provide certainty of the clinically important association between NCCP and oesophageal lesions found. Therefore, the greatest clinical importance of endoscopy is the possibility of diagnosis, including mucosal biopsy and treatment of the morphologic cause of alarm symptoms and the source of haemorrhaging from the digestive tract. Thus, awareness should be accompanied by the knowledge that normal endoscopy does not exclude a gastroenterological cause of NCCP in patients who also have confirmed CAD.

Twenty-four-hour oesophageal pH-metry has been considered the most sensitive and specific test in the diagnosis of GERD and GER-related chest pain. Although 41-43% of patients with NCCP fulfilled the criteria for pathological GERD (Leise et al., 2010), a significant percentage of patients (about 25%) in whom symptoms corresponded with heartburn had rather normal results for 24-hour pH monitoring examinations (Talaie et al., 2009). This discrepancy resulted from the method limitation, as 24-hour oesophageal pH-metry detects acid reflux, and NCCP may also be provoked by the regurgitation of alkaline or neutral gastric content. Therefore, for NCCP diagnosis, especially in patients who are non-responsive to empirical therapy with PPIs, 24-hour simultaneous oesophageal impedance and pH monitoring seems to be more useful, mainly due to the possibility of non-acid gastro-oesophageal reflux (GER) diagnosis (Sifrim & Blondeau, 2006; Sifrim et al., 2009). An additional but practically the most valuable feature of this tool is the possibility of SI and SAP analysis. These enable the evaluation of the relationships between symptom occurrence and oesophageal function disorders which are not only related to the regurgitation of hydrochloric acid. Only such a proven relationship gives an acceptable probability that oesophageal disorders are truly the reason for recurrent symptom episodes, and has been the basis of the identification of "GER-related" and "non-GER-related" chest pain (Dickman & Fass, 2006; Fass & Dickman, 2006; Fass & Navarro-Rodriguez, 2008). One of the oldest tests estimating the

associations between chest pain occurrence and oesophageal acidification is the Bernstein test. Recently, it has not been practically applied, but formerly it was widely used, not only as a diagnostic tool, but primarily in scientific investigation (Chauhan et al., 1996; Makk et al., 2000; Rosztóczy et al., 2007; Schofield et al., 1987, 1989).

Stationary oesophageal manometry, as well as recently introduced high resolution oesophageal manometry, has minor importance in NCCP diagnosis, mainly due to difficulties with confirming the association between chest pain episodes and motility disorders, and the still unsatisfactory treatment effects (Fass & Dickman, 2006; Hershovici & Fass, 2010; Nam et al., 2006). However, 24-hour oesophageal function monitoring is potentially more useful, mainly due to the possibility of examining performance during patients' everyday activity, the greater probability of symptom occurrence during examination and the possibility of correlating their presence with oesophageal disorders (using an SI index or SAP). Moreover, there is now the opportunity to evaluate oesophageal pH and motility correlation on the basis of a greater number of analysed parameters in computer software. On the other hand, the usefulness of both oesophageal pH-metry, impedance examination and 24-hour oesophageal manometry is restricted to patients with daily, or at least every two days, symptom prevalence (Singh et al., 1992). Diagnosis of an NCCP source using 24-hour pH-metry or manometry has been obtained in 46% of patients in whom symptoms occurred at least once per day and only in 11% of subjects with chest pain of less frequency (Janssens et al., 1986). In the study by Eslick (2008), following examination of the most numerous population of patients with non-GER-related chest pain to have been assessed in this way, the distribution of oesophageal motility abnormalities was as follows: normal manometry in 70%, nutcracker oesophagus (14.4%), non-specific oesophageal motor disorder (10.8%), diffuse oesophageal spasm (3%), and other (1.8%). In other papers, nutcracker oesophagus was the most prevalent oesophageal dysmotility in patients with chest pain (Fass & Dickman, 2006; Fornari et al., 2008). Some authors have reported a greater prevalence of oesophageal motility disorders in patients admitted due to chest pain having a normal coronary angiogram than in patients with CAD (Adamek et al., 1999; Battaglia et al., 2005). Whereas, it has not only been my own experience, based on patients non-responsive to empirical therapy with PPIs, which has shown a similar frequency of oesophageal dysmotility in patients both with and without significant coronary artery narrowing (Budzyński, 2010b; Cooke et al., 1998).

As has been mentioned, the clinical usefulness of oesophageal motility examination does not seem to be of great value (Dickman & Fass, 2006; Fass & Dickman, 2006; Nam et al., 2006). Trials involving the provocative use of ergonovine, tensilon, bethanechol and pentagastrin, or oesophageal extension with a balloon have not improved diagnostic efficacy either. My own experience has shown the clinical usefulness of exercise-provoked oesophageal dysmotility diagnosis using simultaneous oesophageal manometry and ECG monitoring during a treadmill stress test. Some exercise-provoked oesophageal motility disorder appeared in 22% of patients with recurrent angina-like chest pain non-responsive to empirical therapy with PPIs (Budzyński et al., 2010; Budzyński, 2010a). The occurrence of angina-like chest pain, oesophageal acidification for more than 10 s, and increased simultaneous contractions above 55% during a treadmill stress test had greater than 80% specificity for diagnosing GER-related and non-GER-related chest pain. The practical message coming from these observations was that patients with recurrent chest pain, who did not report e.g. chest pain during a treadmill stress test, have a low (20%) probability of recognizing an oesophageal reason for their symptoms (Budzyński, 2010a).

High frequency intraluminal ultrasound (HFUS) is an available but rarely used examination, which makes it possible to assess the oesophageal muscle wall thickness in order to evaluate the longitudinal muscle contraction and oesophageal shortening in patients with oesophageal symptoms, including NCCP. Studies conducted using this technique suggest that prolonged oesophageal wall thickening can be connected with chest pain and heartburn episodes (Boesmans et al., 2010; Sifrim & Blondeau, 2006; Sifrim et al., 2009). This examination has also helped to exclude oesophageal ischaemia from the mechanism of chest pain which is gastroenterological in origin (Hoff et al., 2010).

The possibility of having so many gastroenterological examinations for chest pain source diagnoses may lead to problems with making the correct choice. The practical diagnostic algorithm for NCCP presumed to be oesophageal in origin has been proposed by Fass and Navarro-Rodriguez (2008). In all patients with a suspected gastroenterological source of chest pain, after the exclusion of a cardiac origin, they suggest analysing the presence of alarm symptoms (e.g. fever, stomach pain at night, weight loss, anaemia, and signs of bleeding from the digestive tract). If any of these is present, a panendoscopy should first be conducted and treatment should be chosen depending on the diagnosis. In patients without alarm signs, symptom evaluation and testing with PPIs was proposed as the first diagnostic step. In responders to empirical therapy, PPIs should be continued. In patients who fail this test, oesophageal pH-metry "on-therapy", manometry and other gastroenterological investigations, including psychiatric assessment, should be considered.

Careful application of this algorithm in patients with CAD is justified by the proven overlapping of oesophageal chest pain sources in about 30-46% of patients with CAD and cardiac syndrome X (Budzyński et al., 2008; Dobrzycki et al., 2005; Hewson et al., 1990; Oranu & Vaezi, 2010; Singh et al., 1992). Moreover, about 20% of all myocardial ischaemia episodes in patients with CAD correlated with pathological acid gastro-oesophageal reflux episodes, and were recognized as reflexive myocardial silent ischaemia or ischaemic cardiac chest pain due to cardio-oesophageal reflex activation (Dobrzycki et al., 2005). In light of these neurally-mediated cardio-oesophageal interrelationships, a comparison of the coronary reserve in a non-invasive evaluation before and after empirical therapy with PPIs seems to be worth recommending in stable CAD patients, before the next coronarography performance. A decrease in the signs of myocardial ischaemia after one- or two-week-long therapies with PPIs may help to recognize exacerbation of myocardial ischaemia due to oesophageal chemo- receptor activation, which is possible in about half of patients with CAD or cardiac syndrome X (Budzyński et al., 2008; Chauhan et al., 1996; Rosztóczy et al., 2007; Świątkowski et al., 2004). In non-responders to PPI therapy, similarly to patients with NCCP, endoscopy, oesophageal impedence with pH-metry, oesophageal manometry with or without exercise provocation, as well as psychiatric examination, might be helpful (Fass & Navarro-Rodrigues, 2008; Katerndahl, 2004).

6. Treatment

Once the accurate diagnosis of the source of angina-like chest pain has been established, a specific therapy should be recommended. If recurrent chest pain originates only from the heart, due to either ischaemic cardiac or non-ischaemic cardiac disease, typical anti-angina pharmacotherapy and/or myocardial revascularization should be recommended, taking into account the results of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial. In patients with refractory angina diagnosed as cardiac

in origin, a number of methods have been proposed (Kones, 2010). They are as follows: percutaneous myocardial laser revascularization (PMLR) (McGillion et al., 2010); spinal cord stimulation (SCS) (Lanza et al., 2011); enhanced external counterpulsation (EECP); percutaneous application of low frequency ultrasound, i.e. mechanical shock waves with ECG gating; angiogenesis stimulation by the VEGF gene and CD34+ stem cell therapy; etc. Individuals with angina-like chest pain with normal coronary angiogram and patients with CAD and overlapping gastroenterological symptoms may achieve symptomatic improvement after therapy oriented to oesophageal disorders (Phan et al., 2009). Such therapy may consist of long-term treatment with PPIs, therapy with calcium antagonists (Budzyński, 2010a; Budzyński et al., 2010), *Helicobacter pylori* eradication (Budzyński, 2011), as well as tricyclic antidepressants (Eslick, 2008; Fass, 2008; Fass & Navarro-Rodriguez, 2008), selective serotonin reuptake inhibitors (citalopram, sertraline) or trazodone (Broekaert et al., 2006). Recent studies have also indicated the favourable effect of theophylline (Rao et al., 2007), botulinum toxin (Achem, 2008; Fass & Navarro-Rodriguez, 2008), acupuncture (Dickman et al., 2007b; Macpherson and Dumville, 2007; Pfab et al., 2011), melatonin due to its positive cardiological and gastroenterological action (Dominiguez-Rodriguez et al., 2009; Konturek et al., 2008; Pereira, 2006), hypnotherapy (Jones et al., 2006; Palsson and Whitehead, 2006), transcutaneous electrical nerve stimulation (TENS) (Borjesson et al., 1998), oesophageal dilatation, oesophagomyotomy and Nissen fundoplication (Achem, 2008; Dickman & Fass, 2006; Phan et al., 2009).

The outcome of long-term therapy with PPIs in patients with NCCP has been widely studied (Bautista et al., 2004; Cremonini et al., 2005, 2010; Dickman et al., 2005; Dickman & Fass, 2006; Liuzzo et al., 2005; Wang et al., 2005). These drugs have shown a favourable effect in 80% of patients with "GER-related" chest pain (Dickman & Fass, 2006). The relative risk reduction for continued chest pain after PPI therapy was 0.54 (95% CI, 0.41-0.71), with an NNT amounting to 3 (Cremonini et al., 2005). The recent meta-analysis by Cremonini et al. (2010) has also shown an advantage with therapy using a PPI over a placebo with an odds ratio of 3.75 (95% CI, 2.78-4.96), as well as a high placebo response amounting to 18.85% (range 2.94%-47.06%). Successful therapy with PPIs is most likely in patients with a GERD diagnosis (Gąsiorowska et al., 2009; Oranu & Vaezi, 2010; Seo et al., 2010). Among these subjects, acid exposure time (AET), symptom association probability (SAP), and the symptom index (SI) obtained from 24-hour oesophageal pH-metry or 24-hour oesophageal impedance with pH analysis are considered the predictors of a favourable therapeutic outcome (Kushnir et al., 2010).

Until now, there have only been a few works evaluating the role of therapy with PPIs in patients with CAD and recurrent chest pain suspected to be non-cardiac in origin and overlapping ischaemic, cardiac-derived chest pain (Budzyński et al., 2008; Dobrzycki et al., 2005; Liuzzo et al., 2005; Mehta et al., 1996; Świątkowski et al., 2004). All of them, including our own work, have evidenced a decrease in chest pain severity and amelioration in health-related quality of life estimated using the SF-36 survey, as well as an improvement in ECG signs of myocardial ischaemia, both during a treadmill stress test (a reduction in subject percentage with a significant decrease in ST interval during the stress test) and during 24-hour ECG Holter monitoring (a decrease in the number of ST-segment depression episodes and total duration of ischaemic episodes-total ischaemic burden) after therapy with PPIs. Liuzzo et al. (2005), studying a veteran patient population with documented CAD, showed through multivariate analysis and proton pump inhibitor therapy that they could independently predict a significant reduction in the prevalence of patients experiencing

chest pain (OR = 0.09), emergency department visits (OR = 0.15), and hospitalization (OR = 0.14) for chest pain. On the other hand, our own results have shown that the mentioned favourable PPI effect on the angina pectoris course in patients with CAD should be carefully interpreted because it might not only result from the decrease in cardio-oesophageal reflex activation and therapy with aspirin-induced gastropathy, but also from the increase in nitric oxide bioavailability observed after therapy with rabeprazole in an open-label trial (Kłopotcka et al., 2006), as well as the increase in the beta-endorphin plasma level revealed for omeprazole in a randomized, double-blind, placebo-controlled, crossover study (Budzyński et al., 2010).

As has been mentioned, besides a decrease in oesophageal acid exposure time and a reduction in GER-related myocardial ischaemic episodes, PPIs may also improve the course of angina-like chest pain by the alleviation of symptoms related to gastric disease (gastric and duodenal ulcer disease), by preventing and treating aspirin-induced gastropathy, as well as by reducing the risk of haemorrhagic complications from the upper part of the digestive tract and the prevention of secondary anaemia (ACCF, 2010; Bhatt et al., 2008; Hsiao et al., 2009). Tailored PPI prescription should prevail over the generalized in their recommendation for use with patients on dual anti-platelet therapy because of reported and still not definitely excluded potentially life-threatening interactions between PPIs and anti-platelet drugs (clopidogrel, aspirin). Pantoprazole or esomeprazole should be chosen for gastroprotection or time intervals between respective medicines should be recommended (ACCF, 2010; Bhatt et al., 2008). The easiest method for the last option is the recommendation of PPIs in the morning and clopidogrel in the evening.

In patients with recurrent chest pain and GERD diagnosed using oesophageal pH/impedance monitoring and non-responsive to PPIs, many other kinds of therapy have been proposed, including the following: doubling the PPI dose, switching to another PPI, adding histamine type 2-receptor antagonists at night, baclofen recommendation, as well as laparoscopic or open surgery (Dickman & Fass, 2006; Hershcovici & Fass, 2010; Kushnir et al., 2010; Oranu & Vaezi, 2010; Labenz, 2010). The exclusion of eosinophilic oesophagitis in patients with NCCP and aged under 45, atopy or dysphagia might also be helpful (Garcia-Compeñan et al., 2011). Dickman et al. (2007b) found acupuncture added to a single dose of PPI to be more effective than doubling the proton pump inhibitor dose in controlling GERD-related symptoms in patients who had failed with standard dose proton pump inhibitors.

Calcium antagonists, such as verapamil, diltiazem, nifedipine and amlodipine, have mainly been used in therapy for NCCP due to hypertensive oesophageal motility disorders diagnosed using stationary manometry (Dickman & Fass, 2006; Fass & Navarro-Rodriguez, 2006). The reported effects of these drugs in patients with recurrent angina-like chest pain were ambiguous. Some studies have shown a favourable outcome for this group of drugs, some have not confirmed it (Dickman & Fass, 2006; Eslick et al., 2005; Eslick, 2008; Fass & Dickman, 2006). Our own, recently published investigation has shown that patients with recurrent angina-like chest pain non-responsive to treatment with PPIs and an established diagnosis of exercise-provoked oesophageal spasm (EPOS), for whom a calcium antagonist was recommended due to exercise-provoked oesophageal spasm, had a significantly lower risk of hospitalization due to suspected acute coronary syndrome in the 2.7-year follow-up period than the remaining patients (NNT = 3.5) (Budzyński et al., 2010). In my own work it has been documented that Hp eradication had a similar favourable outcome (NNT = 2.7) (Budzyński, 2011). The rationales behind this therapy were the above-cited role of this infection in chest pain pathogenesis both cardiac and gastroenterological in origin.

Psychiatric disorders and anxiety focusing on the heart are common in patients with NCCP (Achem, 2008; Dickmann & Fass, 2006; Fass & Navarro-Rodriguez, 2008; Katerndahl, 2004). They may act as individual factors or via the increase in visceral hypersensitivity. Some studies have shown oesophageal motility abnormalities as markers of depressive or panic disorders. The last were found in 80% of patients with NCCP and oesophageal motor dysfunction and in 30% of subjects with a normal coronary angiogram and oesophageal examinations (Dickman & Fass, 2006). Eslick et al. (2005) have even recommended empirical therapy with tricyclic antidepressants in patients with recurrent chest pain non-responsive to PPIs. The rationale behind such a recommendation is that antidepressants act as pain modulators. In patients with NCCP, behaviour therapy involving trazodone, imipramine, amitriptyline, nortriptyline, citalopram, desipramine and sertraline was used for this purpose (Broekaert et al., 2006; Eslick, 2008; Fass, 2008; Fass & Navarro-Rodriguez, 2008). Their clinical efficacy was confirmed both in uncontrolled and in randomized, placebo-controlled trials. However, the prescribing of these drugs should always be carried out carefully, because of the potential cardiovascular risk of tricyclic antidepressants connected with their adverse effects, such as prolonged QT intervals, hypertension, postural hypotension, and effects on heart rate variability (Hamer et al., 2011). Probably because of this, non-pharmacological methods which could potentially be efficient in subjects with NCCP have been investigated, such as hypnotherapy, behaviour therapy, and acupuncture (Dickman et al., 2007b; Pfab et al., 2011; Yin and Chen, 2010; Zhang et al., 2010). Acupuncture has had a favourable effect on gastric emptying, oesophageal motility, and in patients with GERD, a potential substrate of non-cardiac chest pain. In the study by Macpherson and Dumville (2007), 42% of the patients investigated with a diagnosis of NCCP made in a Rapid Access Chest Pain Unit reported that they would consider acupuncture, 36% reported that they would not, and 22% did not know. Moreover, in the pilot study by Gąsiorowska et al. (2009), a favourable effect of 18 Jorei sessions (a kind of meditation) during six weeks in comparison to waiting-list control patients with functional chest pain was found. The clinical outcome of the mentioned methods is, among other things, explained by a decrease in visceral hypersensitivity, for which one of the mediators may be endogenous opioids, one of the potential pathways of the effect of PPIs (Budzyński et al., 2010). However, it should be checked for each patient as to whether his or her panic or depressive symptoms are the true cause of chest pain recurrence or its cofactor, and not an effect of symptom duration chronicity and the lack of an appropriate diagnosis.

However, particularly in populations with high cardiovascular risk, the appropriate control of cardiovascular risk factors is very important in therapy for patients with angina-like chest pain. The recent study by Leise et al. (2010) has shown that patients with recurrent angina-like chest pain which is gastroenterological but unknown in origin (NCCP-U), in spite of generally being considered as having low cardiac morbidity and mortality, may ultimately show a higher cardiovascular and non-cardiovascular death risk. In this analysis, whose results should still be interpreted with limitations, the NCCP group with a diagnosis of gastrointestinal disorder displayed less overall survival at all time points, specifically 70.1% at 10 years and 51.8% at 20 years, compared with their NCCP-U counterparts. The independent death risk factors in adjusted univariate analysis using Cox's proportional hazards model were as follows: age, the Charlson comorbidity index, previous CABG, and previous valvular disease. No specific cardiac or gastroenterological tests or their absence was associated with mortality. The authors explain their observations by the effect of the coexistence of gastroenterological disorders with latent non-ischaemic cardiovascular

disease, coronary artery spasm (Chang et al., 1988; Makk et al., 2000; Manfrini et al., 2006; Rasmussen et al., 1986), microvascular disease (cardiac syndrome X) or at least endothelial dysfunction. An important aspect might also be an overlapping of risk factors for both systems' diseases, such as obesity, obstructive sleep apnoea, hypertension, smoking, and diabetes mellitus.

On the other hand, the study by Leise et al. (2010) has also shown that proper management of patients with recurrent chest pain which is extracardiac in origin is still a great challenge for physicians. During a 20-year follow-up period since an initial visit to an emergency department due to a recurrent chest pain experience, 49% of patients sought subsequent care from the emergency department, 42% had repeated cardiology evaluations, and only 15% were seen by a gastroenterologist. Thirty-eight percent underwent oesophago-gastroduodenoscopy, but very few underwent manometry or a pH probe.

7. Study limitations

The main limitations concerning investigations on the pathogenesis, diagnosis and treatment for patients with recurrent angina-like chest pain, both in patients with and without significant coronary artery narrowing, have been the small number of subject groups, which on average included a little over 100 participants. Only in three studies were the subject groups larger. The other limitations have involved the lack of or a short follow-up period, recommendations of different medication and their doses, non-homogeneous definitions of oesophageal disorders, the establishment of different study endpoints, and only single-centre experience presentations.

8. Future research

Further studies should validate the test of empirical therapy with PPIs in patients with CAD. It would also be significant if the mechanisms for the visceral hypersensitivity leading to a decrease in the chest pain threshold could be identified. The evaluation of some new diagnostic methods, including analysis for cerebral evoked potentials, would also be useful. Moreover, it seems to be important to check once more and re-evaluate the appropriate indications for coronary angiography, both because of its costs and its inseparable exposure to procedure-connected health risks and substantial radiation. All the recommended examinations, both cardiological and gastroenterological, should be connected with precise investigations into cardio-oesophageal and other vagally-mediated reflexes and on the determination of factors predicting their clinical importance. New therapeutic methods for recurrent angina-like non-cardiac chest pain should also be investigated, although critical analysis of relationships between benefits and costs should be performed.

9. Conclusions

- Angina-like chest pain is a common problem in health care because of its prevalence, diagnostic difficulties, resource utilization and potential connection with a reduced health-related quality of life and shorter survival times. This symptom is conditioned by biological, psychological and social factors.
- Angina pectoris may be caused by diseases of the cardiovascular system, digestive tract, and other extracardiac disorders which lead to an imbalance between myocardial blood

supply and oxygen requirement (e.g. anaemia or thyrotoxicosis). In respective patients, potential chest pain causes may overlap and influence each other. Therefore, NCCP may be present in patients both with and without heart diseases. However, the main and first purpose of its diagnostic procedures should be to exclude potentially life-threatening origins.

- Digestive tract diseases may cause angina-like chest pain along at least three pathways. Chest pain may originate from: (1) the oesophagus, stomach or gall bladder, due to stimulation of their chemo-, mechano-, and/or thermoreceptors; (2) the heart due to activation of cardio-oesophageal neural reflexes and secondary diminished myocardial perfusion; as well as (3) the heart due to a decrease in myocardial oxygen supply in the course of anaemia, secondary to acute or chronic alimentary tract bleeding, malabsorption, maldigestion, blood sequestration or autoimmunological reactions. *Helicobacter pylori* infection may play a role in all of these mechanisms.
- The misdiagnosis of cardio-oesophageal interrelationships may lead to the progressive acceleration of the course of the disorders of both systems and the intensity of their symptoms. This occurs in at least three vicious circle mechanisms: neural, inflammatory (neuro-immune crosstalk), and the haemorrhagic complications of anti-thrombotic drugs expressed as anaemia.
- The most frequent causes of NCCP are as follows: GERD, oesophageal motility disorders and panic abnormalities. Their diagnosis needs many times to use more advanced and more specialized diagnostic methods than panendoscopy, such as oesophageal impedance, pH-metry, manometry, or endosonography.
- In the diagnosis of recurrent chest pain of possible oesophageal origin, the most important factor is to confirm the relationship between chest pain episode occurrence and oesophageal disorders. Such a possibility is provided by the test of empirical therapy using PPIs (the "omeprazole test") and, in non-responsive cases, 24-hour oesophageal pH-metry, impedance or manometry with SI or SAP analysis. These help to recognize the source of chest pain in 40-80% of patients.
- The usefulness of exercise-provoked oesophageal disorders, such as exercise-provoked gastro-oesophageal reflux or oesophageal spasm, needs to be evaluated. Any further investigations need also to estimate the interrelationships between the course of cardiovascular and gastroenterological tests as predictors of false positives in their outcomes.
- Therapy for recurrent, angina-like chest pain should be based on the detailed diagnosis of its origin (whether cardiac or extracardiac), an assessment of its possible influence on myocardial perfusion, and the control of cardiovascular risk factors.
- Modern cardiac and gastrointestinal diagnostic methods would probably help to better recognize NCCP pathophysiology, facilitating its diagnosis and treatment. However, they will need to be critically evaluated, not only in relation to potential clinical usefulness, but also in accordance with risk-benefit and benefit-cost ratios.

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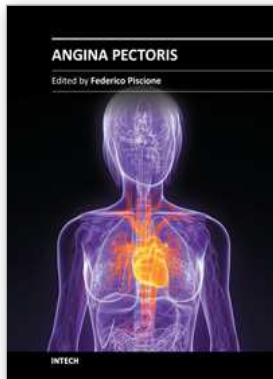
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